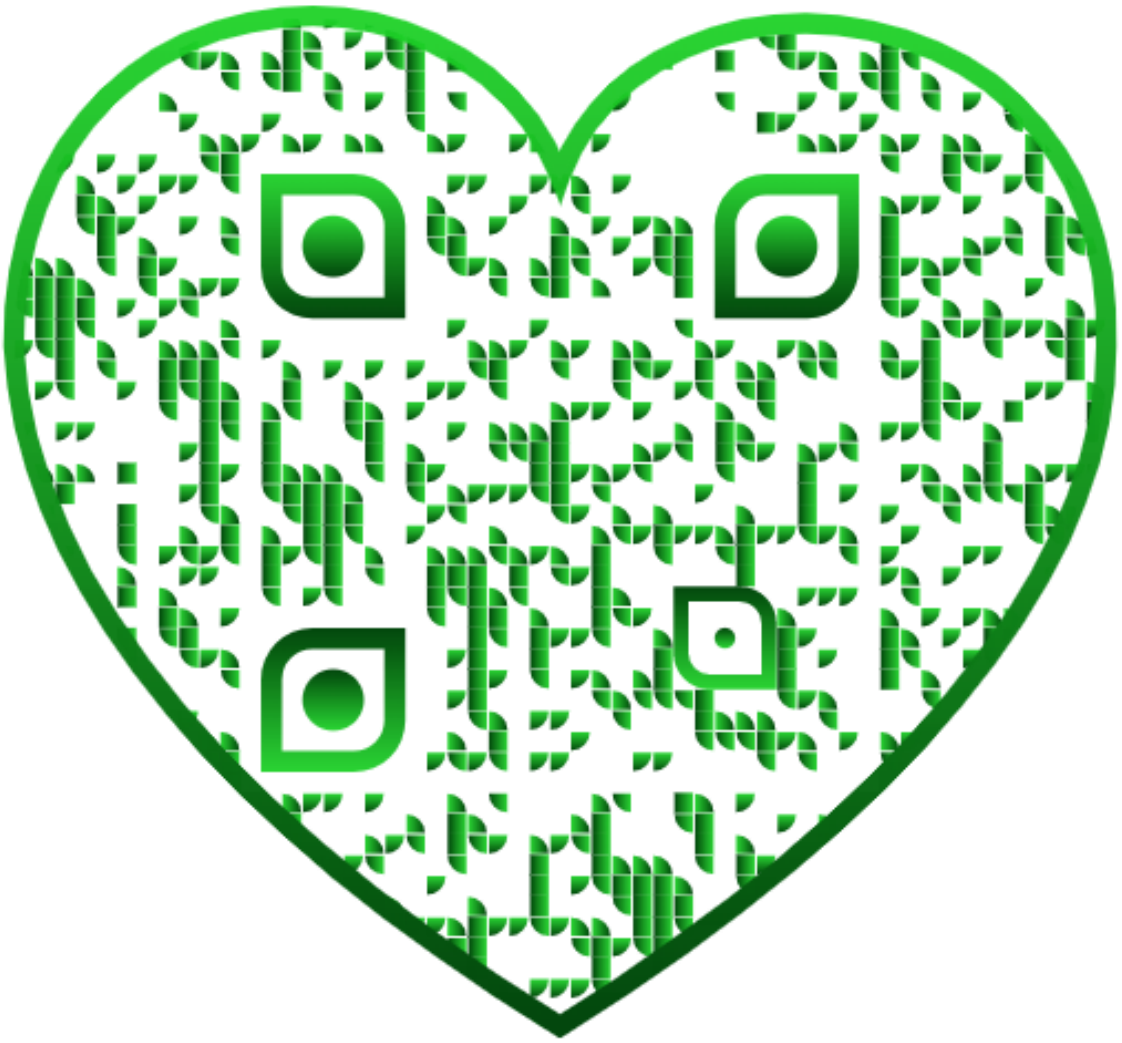
Introduction to Pharmacoepidemiology (Phar 4251)

Sisay E.



Introduction

Origin and Evolution of Pharmacoepidemiology: Historical Background

- Pharmacotherapy 20th century
  - Use of drug increase results increase in ADR
- Drugs must undergo a rigorous evaluation of **safety**, **quality**, **and effectiveness** before they can be sold
- The history of **drug regulation** parallels the history of major **adverse drug reaction "disasters"**

Historical Background…

- **Pure Food and Drug Act of 1906**
  - The **First Federal Drug Law**
  - Prohibited interstate commerce of **misbranded and adulterated *foods, drinks, and drugs***
  - Allowed for seizure and criminal penalties
  - Did not address
    - Food or drug standards
    - False advertising–Inspection of food and drug facilities
  - Enforced by **Division of Chemistry**
  - The bureau became the **Food and Drug Administration in 1930**.

Historical Background…

- **1937 –Elixir of Sulfanilamide**
  - Liquid form of Sulfanilamide produced using **diethyleneglycol** as solvent.
  - Diethyleneglycol = Antifreeze
  - Administered to **mostly children** to treat streptococcal infections
  - Existing laws did not require any kind of pharmacological studies demonstrating that a drug is **safe**.
  - **107** people died

Historical Background…

- **1938-Food, Drug and Cosmetic Act**
  - Extended control to **cosmetics** and therapeutic **devices**
  - Required new drugs to be demonstrated **as safe before marketing.**
  - Eliminated requirement to prove intent to defraud in drug misbranding cases (fraudulent claims)
  - Provided **standards** and safe **tolerances**
  - Authorized factory inspections

Historical Background….

- **1961-Thalidomide Crisis (Tragedy)**
  - Drug for **sleeplessness**
  - Relieved **morning sickness** symptoms in pregnant women
  - Unknown that thalidomide crossed the **placental wall**
  - **Catastrophic results:**
    - Peripheral neuritis - nerve disorder
    - Birth defects –**deafness, blindness, disfigurement, cleft palette, internal defects, phocomelia**

Historical Background….

- **1962-Kefauver-Harris Amendments**
  - Drug Manufacturers were required to prove **drug effectiveness and safety to FDA before marketing.**
  - Advertisements must show complete info **on benefits and risks**
  - Adverse effects must be reported to the FDA

Overview of Drug Development Process

- Drug Discovery
- Screening
- Pre-Clinical Testing
- IND Application
- Phase I Clinical Trials
- Phase II Clinical Trials
- Phase III Clinical Trials
- New Drug Application (NDA)

Phase IV and Beyond

Drug Development Process

- **Therapeutic Drug Discoveries**
  - Determine **target disease**
  - Develop hypothesis for a mechanism of treatment
  - Use **CAD** and 3-D modelling software to begin **evaluating hypothesis**
  - Determine **feasibility** of producing and evaluating the selected compound.

Drug Development Process…

- **Screening**
  - **Combination Chemistry**
    - Make many possible compounds at one time
    - Focus on **quantity** of possible compounds, not purity of each
  - **High Throughput Screening**
    - Test hundreds at a time for activity
  - Process requires serious technology
  - 1 in 10,000 makes it to the market

Drug Development Process…

- **Pre-Clinical Testing**
  - Evaluate **acute** and **short** term **toxicity** in **animals** (one rodent, one non-rodent)
    - Dose at increasingly high levels to induce toxicity
    - Determine **lethal dose**
    - Dose at **normal** levels for short and long term
  - *Assess how drug* ***is absorbed, distributed, metabolized, and excreted in animals***

Drug Development Process….

- **Investigational New Drug (IND)**
  - Request submitted to FDA to **allow** human exposure to the experimental drug.
  - IND is an ongoing file at FDA containing data on drug as it passes through the development process.
- **Phase I Clinical Trials**
  - Few (20-80) healthy volunteer subjects
  - Done by clinical pharmacologist
  - Duration: 1 year
  - Cost: $100,000 -$1,000,000
  - Determine metabolism of the drug, bioavailability
  - Determine safe dosage range in human
  - Determine side effects associated with increasing doses.
  - Gain early evidence on effectiveness

Drug Development Process…

- **Phase II Clinical Trials**
  - Assess **drug's effectiveness** in treating a particular disease or medical condition.
  - Obtain more information on PK of drug and SE, common ADR, safety
  - Determine daily dosage and regimen to be tested more rigorously in phase III
  - 100-300 patient (have target disease) volunteers
  - Done by clinical pharmacologist
  - Duration: 2 years
  - Cost: $10-100 million

Drug Development Process…

- **Phase III Clinical Trials**
  - Company must **consult** with the **FDA** before beginning Phase III.
  - 1,000-3,000 patient volunteers
  - Done by clinician investigator
  - Rigorously evaluate **drug efficacy and safety (toxicity)**
  - Multiple testing sites
  - Duration: 3-3.5 years
  - Cost: $10-500 million
  - At least one of the Phase III studies should be **RCT**

Drug Development Process…

- **New Drug Application (NDA)**
  - Formal proposal for the FDA **to approve a new drug for sale** in the U.S
  - Must provide sufficient evidence for the FDA to decide:
    - Drug is safe and effective
    - Benefits outweigh the risks
    - Proposed labelling is appropriate
    - Manufacturing methods and controls maintain drug identity, strength, quality, and purity

Drug Development Process….

- All other drugs
  - Center for Drug Evaluation and Research (CDER)
- NDA Review Process
  - **Medical** -clinical **protocols**, safety
  - **Biopharmaceutical** -absorption, distribution, metabolism, and excretion
  - **Pharmacology** -toxicity, therapeutic value
  - **Chemistry** -chemical properties
  - Microbiology -anti-infective drugs
  - **Statistical** -results must be significant

Drug Development Process…

- **Registration and Market Launch**
  - NDA must be approved
  - Must prove to FDA that you can safely produce drug
  - Pre-approval inspection
  - 3 production batches
  - Development group justifies development process

	Preclinical	File IND with FDA	Phase I	Phase II	Phase III	File NDA with FDA	FDA		Phase IV
Years	3.5-6.5		1-1.5	2	3 -3.5			15 total	
Test Population	**Laboratory and Animal Studies**		20 -80 healthy volunteers	100 – 300 patient volunteers	1,0000-3,0000 patient volunteers	1000 – 3,000 patient volunteers			
Purpose	**Assess safety and biological activity**		Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions for long term use		Review process approval		Additional post marketing testing
Success Rate	**5,000 compounds evaluated5**			5 enter clinical trial			1 approved		

What is Epidemiology?

- **Epidemiology comes from the Greek words**
  - **Epi** means **"on or upon,"**
  - **Demos** means "**people**,"
  - **Logos** means **"the study of"**
- **Definition of Epidemiology:**
  - "Epidemiology is the study of the **distribution** and **determinants of health-related states or events** in **specified populations**, and the **application** of this study to the control of health problems."
  - Epidemiology Study of the relationships between diseases or any other biological phenomenon and various factors
    - e.g. Lifestyle, environment or social setting, individual traits, etc.)
      - Which can influence their frequency, distribution and evolution

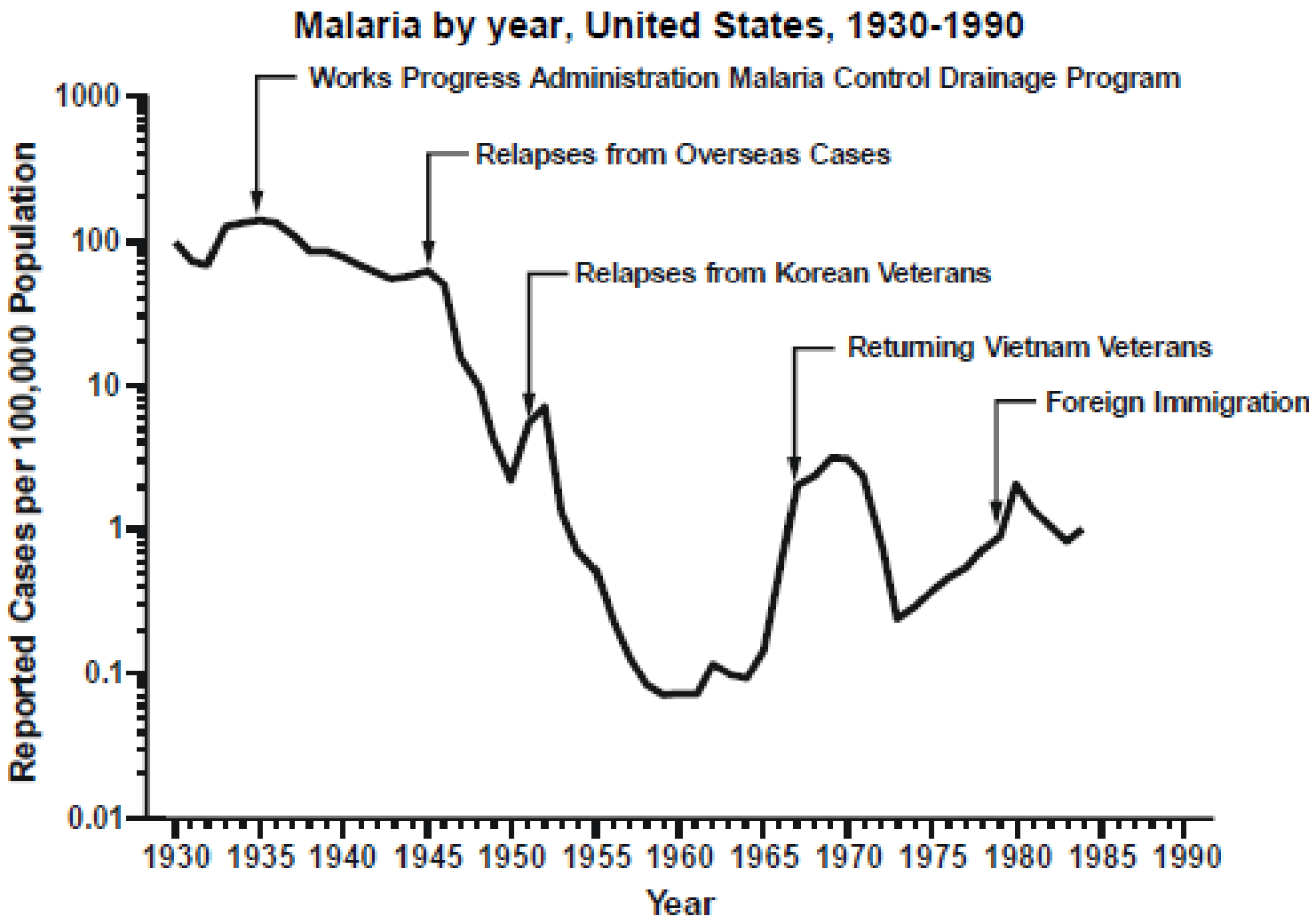
What is Epidemiology?...

- The definition includes several terms which reflect principles of the discipline
- **Study**
  - **Epidemiology is a scientific discipline**
  - Has **scientific methods of inquiry**
- **Distribution**
  - Epidemiology is concerned with the **frequency** and **pattern of health events in a** population

What is Epidemiology?...

- **Frequency**
  - The number of events in a population
  - Rate or risk of disease in the population→ Comparison
- **Pattern**
  - Occurrence of health-related events by time, place, and personal characteristics.
- **Time**
  - Annual, seasonal, and daily or even hourly occurrence

Example of trend



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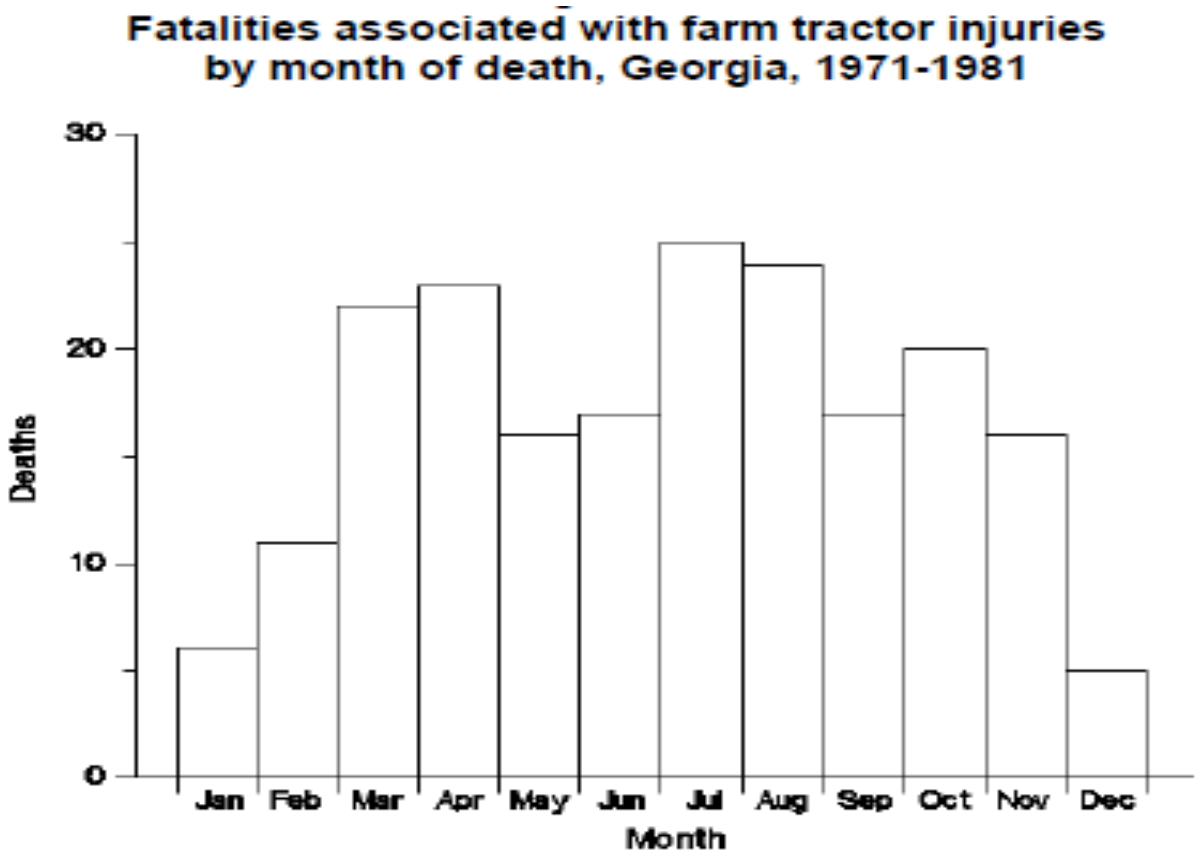
Example of seasonality



What is Epidemiology?...

- **Place**
  - Geographic variation, urban-rural differences, and worksites or schools
- **Personal characteristics**
  - Demographic factors such as age, race, sex, marital status, and socioeconomic status, as well as behaviors and environmental exposures
- **Determinants**
  - Epidemiology is also used to search for **causes** and **other** factors that **influence the occurrence** of health-related events

What is Epidemiology?...

- **Health-related states or events**
  - Epidemiology was originally **concerned** with **epidemics** of **communicable** diseases
  - **Endemic** communicable diseases
  - **Noncommunicable** infectious diseases
  - **Chronic** diseases
  - **Injuries**, birth defects, maternal-child health, occupational health, and
  - Environmental health
  - **Behaviors** related to health and well-being (amount of exercise, seat-belt use, etc.)

What is Epidemiology?....

- **Specified populations**
  - ***Epidemiologists*** *vs* ***physicians*** *in clinical practice*
    - **Both** are concerned with **disease control**
    - But they differ greatly in how they view "***the patient***"
    - **Clinicians** are concerned with the **health of an individual**
    - **Epidemiologists** are concerned with **the collective health of the people in a community or other area**

What is Epidemiology?...

- **Example:** Patient with **diarrheal** disease
  - **Clinician** focuses on **treating** and **caring** for the **individual**
  - **Epidemiologist** focuses on;
    - Exposure (action or **source** that caused the illness)
    - Number of **other** persons who may have been similarly exposed
    - The **potential for further** spread in the community
    - **Interventions** to prevent additional cases or recurrences.

What is Epidemiology?...

- **Application**
  - Epidemiology is more than "the study of."
    - E.g. Epidemiology to drug:
      - Adverse drug reaction reporting
      - Post marketing surveillance studies
      - Clinical drug trials

Types of Epidemiological stsudies

- **Descriptive epidemiology:**
  - Concerned with **describing the general characteristics of the distribution of disease**, particularly in relation to person, place, and time
  - Studies of ***'What', 'Who', 'When', and 'Where'*** *of health-related events*
  - The objective is to describe a population (e.g. drug utilization studies)
- **Analytic epidemiology:**
  - Process of testing a specific hypothesis about a potential **exposure and an outcome of interest.**
  - Studies '***Why'*** *and* ***'How'*** of health events
  - The objective is to study the associations (causal or otherwise) that can exist, within a population, between the occurrence of an event and a given characteristic
    - (e.g. exposure to a risk factor)

Epidemiologic studies…

- **Experimental:**
  - **Investigator determine** the exposure status for each **individual (clinical trial)** or **community (community trial)**
    - Then follow the individuals or communities to detect the **effects** of the exposure
  - **Observational:**
    - **Investigator** simply **observe** the **exposure** and **outcome** status of each study participant

Epidemiologic studies…

- E.g. in 2006 data suggest
  - 100 000 Americans **die** each year from ADRs
  - 1.5 million US **hospitalizations** each year from ADRs
  - 20-70% of ADRs may be **preventable**
  - The **harm** that **drugs** can cause has also led to the development of the field of ***pharmacoepidemiology***

What is Pharmacoepidemiology (PE)?

- The term pharmacoepidemiology contains two components:
  - "Pharmaco" and "epidemiology."
- The joining of the fields of **clinical pharmacology** and **epidemiology** has resulted in the development of a new field called **pharmacoepidemiology**
- **Definitions of PE:**
  - Branch of epidemiology that studies the use and effect of medicines in specific populations.
  - The study of the **use** of and the **effects** of drugs in **large numbers of people**
  - It is an essential field generating data on the safety, efficacy, and effectiveness of drugs.
  - It studies the relationships between patients, diseases, and medicines

What is PE?

- **Population Perspective**
  - Focuses on drug use and health outcomes in large populations
- **Real-world Settings**
  - Observes drug use in routine clinical practice instead of controlled settings
- **Interdisciplinary Approach**
  - Combines epidemiology, pharmacology, and statistics.

What is Pharmacoepidemilogy?...

- PE is concerned with study of the therapeutic effect(s), risk and use of drugs, usually in large populations, using epidemiological methods and/or reasoning
    - Application of epidemiologic knowledge, methods, and reasoning to the study of the effects (beneficial and adverse) and use of drugs in human populations
- PE study the **distribution** and **determinants** of **drug** related **events** in a defined population and the application of this study to **efficacious** drug treatment

What is Pharmacoepidemiology?...

- **Scope of Pharmacoepidemiology**
    - Clinical pharmacology
    - Epidemiology

Scope of Pharmacoepidemilogy in drug regulation

Table 8.1. Scope of pharmacoepidemiology in drug regulation

Stage in life cycle	Examples of possible applications of pharmacoepidemiology
Drug discovery	Identification of potential markets through study of disease distribution and medicines utilization
Drug development	Estimation of potential market size, unmet medical needs, demonstration of efficacy and safety. Selection of likely co-prescribed medicines for interaction studies. Planning safety data collection strategy for the development and post-licensing phases
Orphan drugs	Estimation of prevalence of disease, providing information on other treatments, demonstration of efficacy and safety, demonstrating significant benefit
Licensing	Information on the disease to be treated, existing therapies, safety profile of alternative therapies, demographics of toxicities associated with the medicine. Planning of safety monitoring post-licensing and risk minimization strategies
Post-licensing: pharmacovigilance	An aid to all steps in the pharmacovigilance process: signal detection and evaluation, benefit/risk assessment, measurement of the health effects of action taken to reduce risk
Variation, renewal, reclassification	Evaluation of benefits and risks in new indications. Re-evaluation of benefits and risks when new data are available regarding an established indication. Estimation of market size and use of existing therapies when considering a move to use without prescription
Pharmacoeconomics	Estimation of costs of therapy and benefits in economic terms to support reimbursement or inclusion in formularies

Pharmacoepidemiology Vs. Clinical pharmacology

- **Pharmacology:** Concerned with the study of the **effects of drugs**
- **Clinical pharmacology**: Concerned with the study of the effects of drugs in humans
  - Therapy should be individualized, or tailored to the needs of the specific patient at hand
  - **Individualization** of therapy requires the determination of a risk/benefit ratio specific to the patient at hand

Pharmacoepidemiology vs. clinical pharmacology…

- E.g: consider a **patient** with a serious infection, serious liver impairment, and mild impairment of his or her renal function.
  - Is Gentamicin appropriate for treatment?
  - Knowing gentamicin has a small probability of causing renal disease is not sufficient
  - Patient who has impaired liver function is at a greater risk of suffering from this **adverse effect** than one with **normal** liver function.
- Pharmacoepidemiology can be useful in providing information about the beneficial and harmful effects of any drug
  - Better assessment of the **risk/benefit** balance for the use of **any** particular **drug** in **any** particular **patient**

Pharmacoepidemiology vs. clinical pharmacology

- **Clinical pharmacology (PK+PD)**
  - **Pharmacokinetics**
    - Dose administered of a drug and the serum or blood (ADME)
- **Level achieved**
  - Pharmacodynamics
    - Drug level and drug effect
  - PK + PD allow one to predict the effect one might observe in a patient from administering a certain drug regimen

Pharmacoepidemiology vs. clinical pharmacology

- Pharmacoepidemiology encompasses elements of both of these fields, exploring the effects achieved by administering a drug regimen.
  - It does **not** normally involve or require the measurement of drug levels.
- Specifically, the field of pharmacoepidemiology has primarily concerned itself with the study of ***adverse drug effects***

Pharmacoepidemiology vs. clinical pharmacology…

- Adverse reactions
  - *Type A reactions*
  - *Type B reactions*
- ***Type A reactions***
  - Common
  - Dose-related
  - Predictable, and less serious.
  - Treatment
    - simply reducing the dose of the drug

Pharmacoepidemiology vs. clinical pharmacology…

- Occur in individuals
  - Who received more of a drug than is customarily required
  - received a conventional amount of the drug, but they may metabolize or excrete the drug unusually slowly,
  - Received normal drug levels, but for some reason are overly sensitive to them.

Pharmacoepidemiology vs. clinical pharmacology

- **Type B reactions**
  - Uncommon
  - Not related to dose
  - unpredictable, and potentially more serious.
  - Treatment
    - Require cessation of the drug.

Pharmacoepidemiology Vs. clinical pharmacology…

- Hypersensitivity reactions or immunologic reactions
- Idiosyncratic reaction to the drug
    - Inherited susceptibility (e.g., glucose-6-phosphate dehydrogenase deficiency)
    - Some other mechanism
  - Represent the **major** focus of many pharmacoepidemiology studies of adverse drug reactions

Pharmacoepidemiology vs. clinical pharmacology…

- The usual approach to studying ADR
  - collection of spontaneous reports of drug-related morbidity or mortality
  - Problem -determining causation in case reports
  - This lead to the field of epidemiology
- Specifically, *studies of adverse effects have been supplemented with studies of adverse events.*

Pharmacoepidemiology vs. clinical pharmacology…

- Studies of adverse **effects**
  - *investigators examine case reports* of purported ADR
  - attempt to make a subjective clinical judgment on an *individual basis about* whether the adverse outcome was actually caused by the antecedent drug exposure

Pharmacoepidemiology vs. clinical pharmacology…

- **Studies of adverse events…**
  - Controlled studies are performed
    - Exposed population vs. Unexposed population
  - examining whether the adverse outcome under study occurs more often in an exposed *population than in* an unexposed population
- This marriage of the fields of clinical pharmacology and epidemiology has resulted in the development of a new field: pharmacoepidemiology.

Pharmacoepidemiology versus epidemiology

- *Epidemiology is the study of the* ***distribution and determinants*** **of diseases in populations**
- The field of pharmacoepidemiology uses the techniques of chronic disease epidemiology to **study the use of and the effects of drugs**.
- **Methods of pharmacoepidemiology**
  - useful in performing the clinical trials of drugs
  - post marketing drug surveillance (major application)

Pharmacoepidemiology Vs Epidemiology

- **Pharmacoepidemiology**
  - Relatively new applied field
  - Bridging between clinical pharmacology and epidemiology
- **Pharmacoepidemiology borrows**
  - Its **focus** of inquiry from clinical pharmacology,
  - Its **methods** of inquiry from epidemiology
  - It applies the methods of epidemiology to the content area of clinical pharmacology

Aim of Pharmacoepidemiology

- **Signal Generation:**
  - Most commonly associated with ADR but also use to detect new applications
    - Example: Minoxidil: 1st indicated for hypertension but case report (signal generation) soon identified it causes hirsutism in a number of patients, side effect was investigated and now it is marketed for purpose mainly stimulation of hair growth
- **Risk Quantification:** ADR (often require large sample size)

Sources of Data in Pharmacoepidemiology

- **Administrative Databases**
  - Electronic records of health care visits, pharmacy claims, and insurance data.
- **Electronic Health Records**
  - Digitized patient's health records that allow researchers to follow-up on usage and compare different treatments
- **Surveys**
  - Questionnaires and interviews with patients or physicians to gather information about drug use.
- **Clinical Trials**
  - Controlled studies that investigate the safety and efficacy of new drugs.

Purpose of Pharmacoepidemiology

- **Data acquisition and Analysis**
  - Identify uses, patterns, and effects of drugs in populations and subgroups
- **Risk Assessment and Management**
  - Identification of risk factors and implementation of interventions for better population health outcomes
- **Drug Safety Evaluation**
  - Monitor drug safety for all types of marketed drugs
- **Health Policies and Decisions**
  - Produce evidence-based data to create and shape health policies.

Aim of Pharmacoepidemiology…

- **Hypothesis testing:**
  - Require the use of **comparison group** to determine whether there are difference in variable of interest (risk factor, trait, characteristic, drug exposed, or clinical conditions)
  - Statistic method are used to assess whether the observed difference could have occur by chance alone
  - Conclusions about relation b/w exposure to a drug and clinical event thus based on the ability to **reject the null hypothesis,** postulating that the 2 group are no difference with regard to either the drug exposure or the clinical event

Contributions of Pharmacoepidemiology

1. Information which **supplements** the information available from premarketing studies

   – Better quantitation of the incidence of known adverse and beneficial effects

   - Higher precision
   - In patients not studied prior to marketing, e.g., the elderly, children, pregnant women
   - As modified by other drugs and other illnesses
   - Relative to other drugs used for the same indication

Contributions of Pharmacoepidemiology

2. **New** types of information not available from pre-marketing studies
   - Discovery of previously **undetected** adverse and beneficial effects
     - Uncommon effects
     - Delayed effects
   - **Patterns** of drug utilization
   - Effects of drug **overdoses**
   - Economic implications of drug use
3. **General** contributions of pharmacoepidemiology
   - **Reassurances** about drug safety
   - **Fulfilment** of ethical and legal obligations

Reasons to perform Pharmacoepidemiology

- ***(A) Regulatory***
  - Required
    - To obtain earlier approval for marketing
    - As a response to question by regulatory agency
    - To assist application for approval for marketing elsewhere

Reasons to perform Pharmacoepidemiology…

- ***(B) Marketing***
  - To assist market penetration by documenting the safety of the drug
  - To increase name recognition
  - To assist in repositioning the drug
    - Different **outcomes**, e.g., quality-of-life and economic
    - Different types of **patients**, e.g., the elderly
    - New indications
    - Less restrictive labeling

Reasons to perform Pharmacoepidemiology…

- (4) To protect the drug from **accusations** about adverse effects
- ***(C) Legal***
  - In anticipation of future product liability litigation

Reasons to perform Pharmacoepidemiology…

- ***(D) Clinical***
  - Hypothesis testing
    - Problem hypothesized on the basis of **drug** structure
    - Problem **suspected** on the basis of preclinical or premarketing human data
    - Problem suspected on the basis of **spontaneous** reports
    - Need to better **quantitate** the frequency of **adverse reactions**

Reasons to perform Pharmacoepidemiology…

- Hypothesis generating- need depends on:
  - Whether it is a **new** chemical entity
  - The **safety** profile of the class
    - Penicillin allergy → New Penicilline derivative
  - The relative safety of the drug within its class
  - The formulation
  - The disease to be treated, including;
    - its duration
    - its prevalence
    - its severity
    - whether alternative therapies are available

Application of Pharmacoepidemiology

- Estimation of risk of drug use
- Use in patient counseling
- Formulation of public health policy decision
- Formulation of therapeutic guidelines and discovery of new indications
- Facilitation of pharmaco-economic evaluation

Challenges in Pharmacoepidemiology

- **Data Quality**
  - Ensuring accurate and complete data collection from various sources and minimizing bias
- **Multiple Drug Use**
  - Differentiating the effects of multiple drugs used by patients with complex conditions
- **Population Diversity**
  - Including diverse populations in research to ensure generalizability and equity
- **Ethical Concerns**
  - Addressing the ethical issues involved in using people's health data, especially regarding privacy and data safety

Study Designs in Pharmacoepidemiology

Sisay E.

Sources of Knowledge

- Two major approaches of knowing the world:
  1. **Everyday experience and**
  2. **Science**
- **1. Everyday Experience as Sources of Knowledge**
  - **Method of Tenacity**
    - Acceptance of a belief based on the idea that "***we have always known it to be this way"***
    - Automatic acceptance of the prevailing traditional beliefs and customs in which we have been socialized

Sources of Knowledge…

- **Two problems of Tenacity**
  - The information may gain wide acceptance through its familiarity alone
  - Tenacity offers no means for correcting erroneous ideas.
    - *E.g: Is darker colored 'injera' more nutritious?*
- **Method of Authority**
  - If we are naïve to most of the practices what we do, we ask someone in that culture who is supposed to have the knowledge – an authority figure.
    - E.g *a physician may tell us that smoking affects our health.*

Sources of Knowledge…

- **Priori Method**
  - First we develop **general** knowledge, opinion, or belief about the world through the aforementioned methods or personal observation of things around us and then we draw **new** and **specific** conclusion from this general knowledge.
  - Known as a **deductive reasoning**
    - ***Example:*** *All men are tall; Alemu is a man; therefore, Alemu is tall.*
    - Logical conclusions may not necessarily lead to correct conclusions.

Sources of Knowledge…

- **Common Sense**
  - Based on our own past experiences and our perceptions of the world
  - The concepts that we have about the world may be seriously misleading
  - May help us deal with the routine aspects of daily life
  - May also form a wall and prevent us from understanding new ideas

Sources of Knowledge…

- **2. Scientific Method as a Source of Knowledge**
  - Science is a body of systematized knowledge
  - In scientific method, **ideas** are **evaluated** and **corrected** through dispassionately observing by means of our bodily senses or measuring devices
  - Science and common sense **differ** in terms of:
    - Use of **conceptual** schemes and theoretical structures
    - The notion of **control**
    - The **explanations** of different observed phenomena

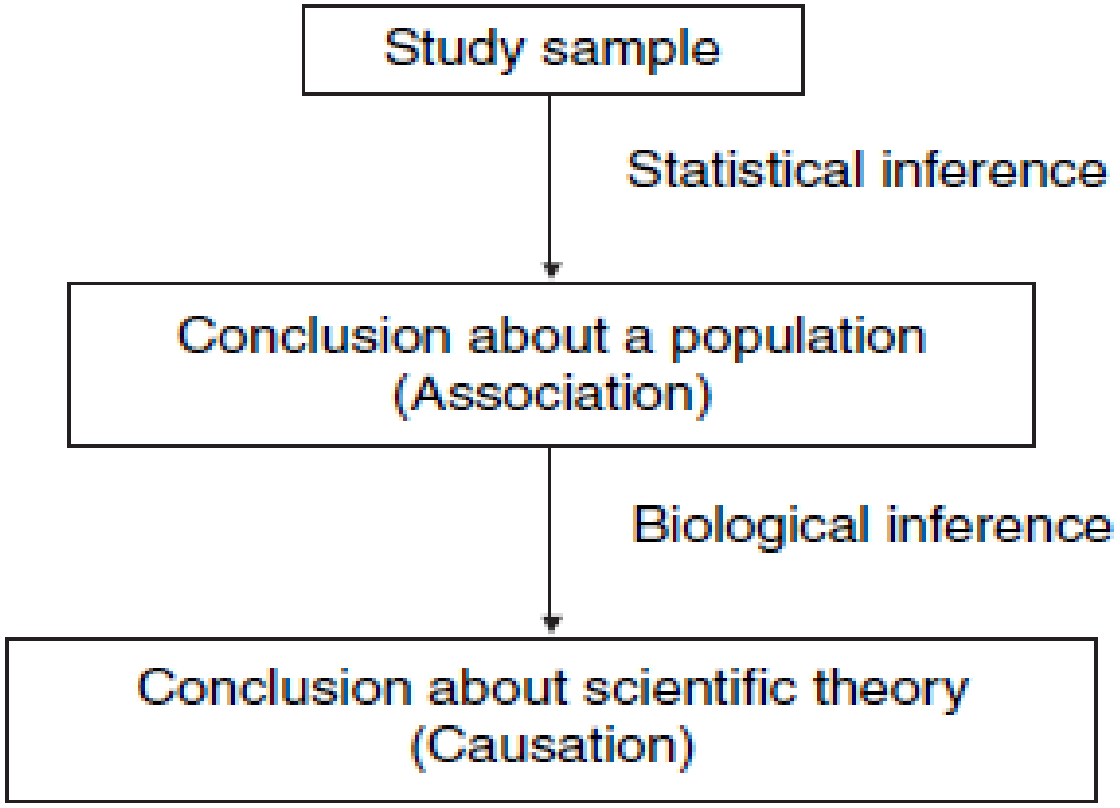
Scientific Method as a Source of Knowledge…

- Scientific research follows logical steps, which include:
  - Defining the problem
  - Making tentative explanations
  - Gathering information
  - Testing the validity of the hypothesis
  - Making conclusions as to whether the hypothesis can be accepted or rejected

Overview of scientific methods

- The scientific method is a **three-stage** process
  - First, **selects** a group of subjects for study (Sample)
  - Second, **Generalize** and draw a conclusion about a **population**
    - This conclusion is referred to as an **association**
  - Third, drawing a conclusion about **scientific theory or causation**

Overview of scientific methods…



Overview of scientific methods…

- **Example**
  - RCT on the efficacy of enalapril in lowering BP by randomly allocating a total of **40 middle-aged hypertensive** men to receive either **enalapril** or **placebo** and observing their BP **six weeks later**
  - **Expected outcome**
    - Enalapril **lower the BP** of the 20 men compared to the BP of the 20 men treated with a **placebo**
  - Study **sample/** subject
    - 40 men → **sample size**
    - **Representative**
      - Middle-aged hypertensive men (target population)

Overview of scientific methods…

- Conclusion about population or **association**
  - Enalapril lowers BP in middle-aged hypertensive men
- Conclusion about scientific theory or causation
  - Enalapril is an antihypertensive drug in general
- To generalize **Enalapril** lowers BP in middle-aged hypertensive men
  - Rule out the association is not b/c of **chance, bias, confounder and then apply the criteria for the causal nature**

Overview of scientific methods…

- Epidemiological studies aim to provide accurate measures of health related event or states
  - **Error in measurement**
    - Minimize error
    - Assess the impact of error
  - Error → **random + systemic**
- **Random error**
  - When a value of sample measurement diverges from the true population due to chance alone

Overview of scientific methods

- **Chance**
  - **Random error** or variation
  - Sampling error, measurement error, biological variation
  - Perform a statistical test to quantitate the probability that the observed outcome in this study
    - (e.g. enlalpril and placebo taking) **could have happened simply by chance**.
  - "**statistically significant difference**," then one is said to have an *association.*

Overview of scientific methods…

- **Systemic error or bias**
  - Any **systematic error** in the **design**, **conduct** or **analysis** of a study that results in a mistaken estimate of an exposure- effect on the risk of disease/outcome
  - Systematic variation occur **when two study groups** are treated or evaluated **differently**.

Overview of scientific methods…

- **Systemic error or bias…**
  - E.g. **Selection bias → healthy worker effect**
    - In a factory where workers are exposed to **formaldehyde,** those who suffer from eye irritation are most likely to lose their jobs.
    - The remaining workers are less affected and a prevalence study of the association b/n formaldehyde exposure and eye irritation that is done only in the work place may be very misleading.
- **Measurement bias**
  - Specimen from exposed and non exposed (control) are analyzed by different laboratories

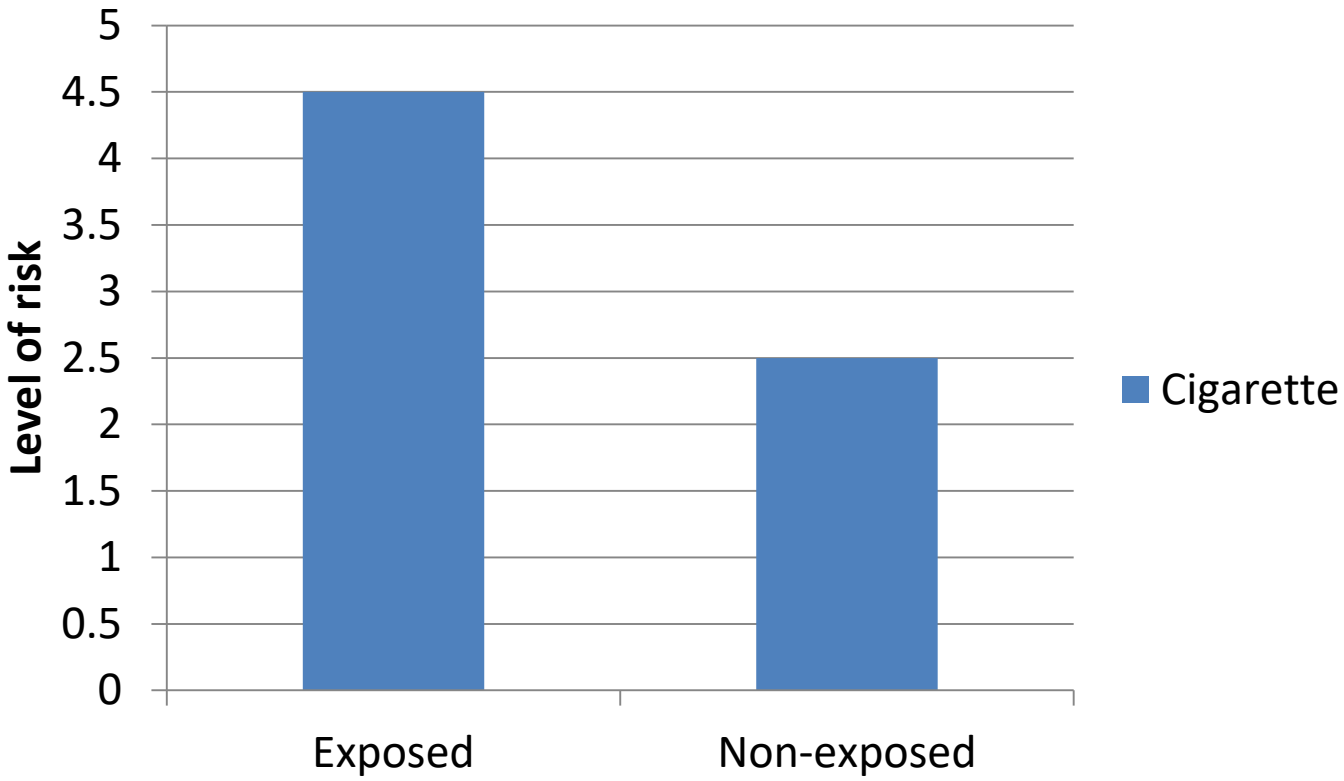
Overview of scientific methods…

- **Recall bias**
  - Differential recall of information by **cases** and **control**
    - E.g: Lack of exercise and heart disease
- **Observer bias**
  - If the investigator, lab technician or participant knows the exposure status
  - Knowledge cause influence
- **Bias** create an **apparent** association where one actually does not exist or can **mask** a true association
  - E.g. Selection bias, Information bias**,** Interviewer bias, Recall bias
- ***NB!*** biases once present, cannot be corrected.
  - *a statistically significant result is no protection against a bias*

Overview of scientific methods…

- Association: estimating risk
  - **Absolute risk**: The incidence of a disease/event in a population
  - **Attributable risk (AR)** or **risk difference or excess risk**:
    - Difference between the risk measured in an exposed population (the absolute risk) and that measured in non exposed population
  - **Relative risk** (RR) (RR<1, RR=1, RR>1)

Total risks of cancer in exposed and non-exposed groups



Overview of scientific methods…

- ***Odds ratio (OR)***: Ratio of two odds, each being ratio of one probability to its complementary probability (OR<1, OR=1, OR>1)
- **Odds:** The probability that an event will occur divided by the probability that it will not occur
- To draw this type of conclusion
  - Requires one to generalize to populations other than that included in the study, including types of people who were not represented in the study sample, such as women, children, and the elderly

Overview of scientific methods….

- **Biological inference**
  - Examine the data at hand in light of all other relevant data in the rest of the scientific literature
  - Make a **subjective** judgment
  - Use "**Criteria for the causal nature of an association**" or "apply **Doll Hill Guideline**,"

Overview of scientific methods….

- There are four basic types of associations
  - **No** association or independent
  - **Artifactual** association (a spurious or false association)
    - Two mechanisms: Chance and Bias
  - Indirect (**confounded**)
  - Causal (**direct** or true)

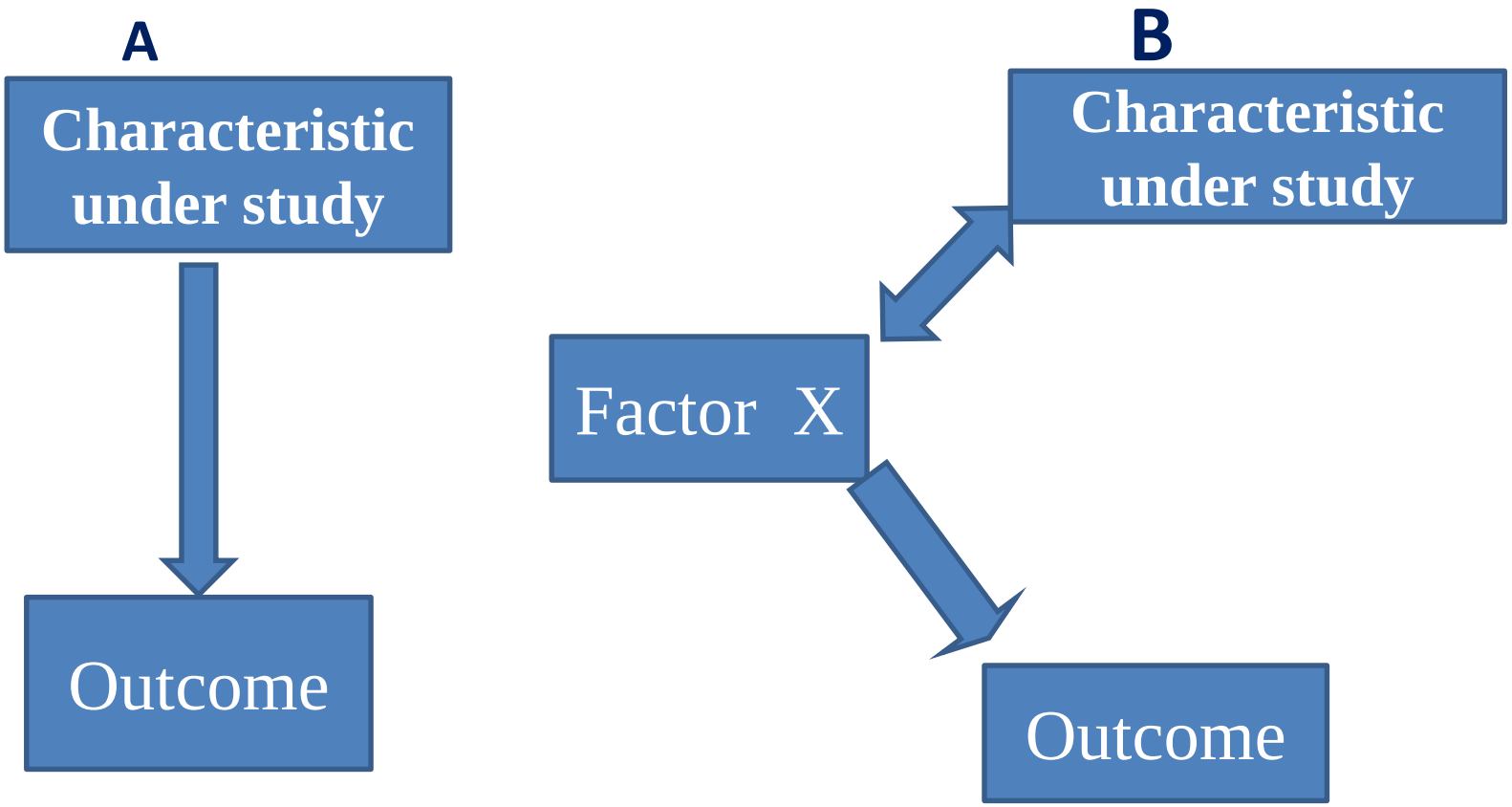
Indirect, or confounded association

- A confounding variable or confounder
  - Is a variable other than the **risk factor** and **outcome** under study
  - Related **independently** to both the risk factor and the outcome variable
  - May create an **apparent** association or **mask** a real one

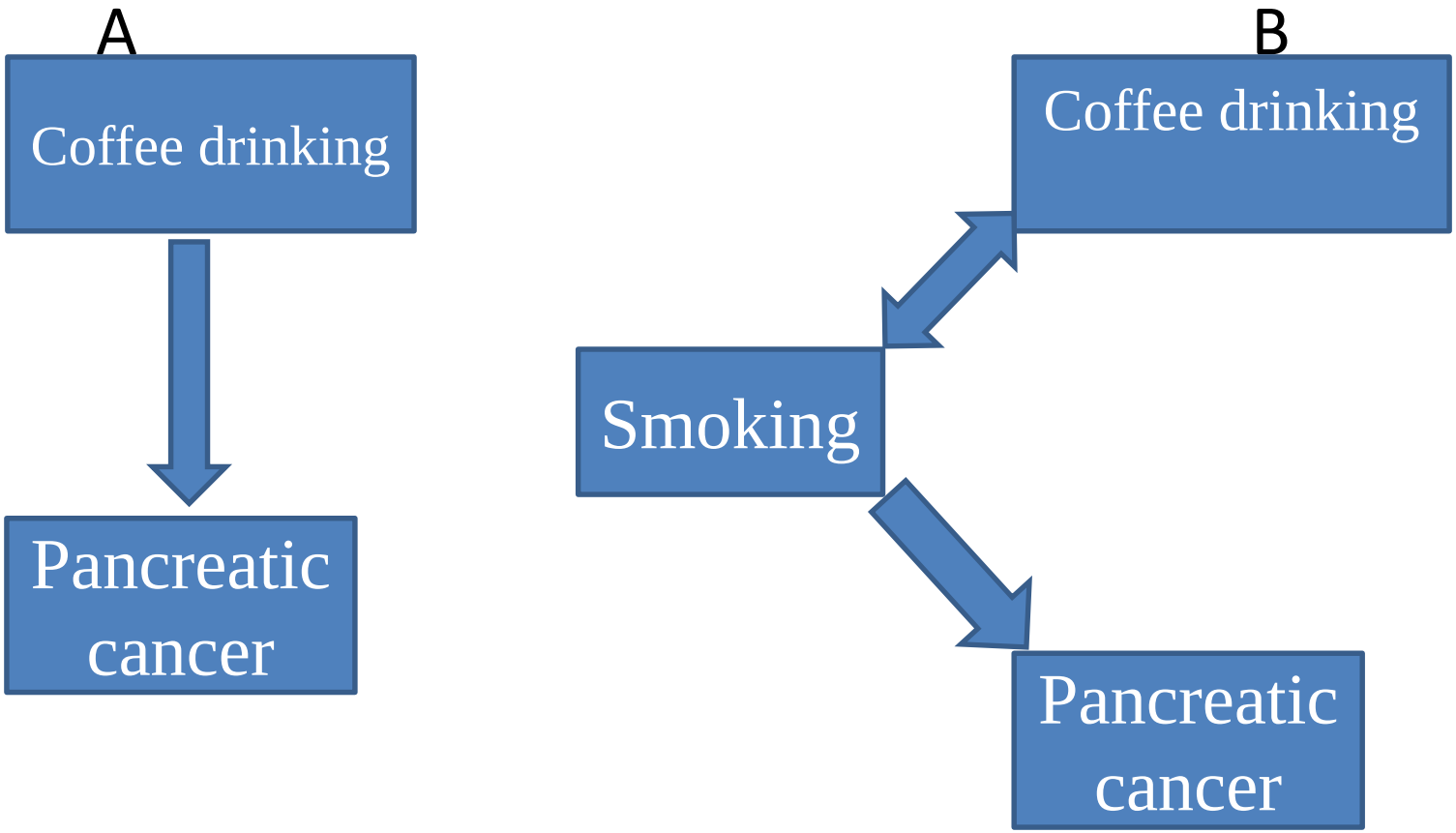
Confounder

- In a study of whether factor **A** is a cause of disease **B**, we say that a third factor, factor **X**, is a confounder if the following are true:
  - 1. Factor X is a **known** risk factor for disease B.
  - 2. Factor X is **associated** with factor A, but is not a result of factor A.
    - E.g 1 McMahon observed an association of **coffee** consumption with risk of **pancreatic cancer**
    - Was the observed association of **coffee** drinking and cancer of the **pancreas** likely to be a **causal** relationship?

A. Causal B. Due to confounding



A. Causal B. Due to confounding



Confounder…

- Smoking (factor X) was a confounder
  - 1. Smoking is a **known** risk factor for pancreatic cancer (disease B)
  - 2. Smoking is associated with coffee drinking, but is not a result of coffee drinking (factor A)
  - ***NB*** ! coffee drinking and cigarette smoking are closely associated (few smokers do not drink coffee)

Confounder…

- **Approaches to control confounding**
  - Random allocation
  - Subject selection
    - Exclusion
    - Matching (case vs control)
- Data analysis
  - Stratification
  - Mathematical modeling

Criteria for the causal nature of an association or "Doll Hill guideline"

- No one of them is absolutely **necessary/ sufficient**
  - For a **causal** association
- The more criteria that are present, the more likely to be a causal association

I. Coherence with existing information or biologic knowledge (biological plausibility)

- Data from other human studies
- Data from animal studies
- Data from *in vitro studies*
- Scientific or pathophysiologic theory

Criteria for the causal nature…

- **Example:**
  - **Cigarettes** could cause lung cancer lung cancer
    - In **animal** data → cigarette smoking is a known carcinogen
    - In **humans**, it is known to cause cancers of the head and neck, the pancreas, and the bladder.
    - ***Thus, it certainly is biologically plausible that cigarettes could cause lung cancer***

Criteria for the causal nature…

II. Consistency of the association or replication of the findings

- Science is reproducibility
  - Different geographic **settings**, study **designs**,
  - Different **populations**, etc.

- **Example**
  - The case of cigarettes and lung cancer,
- One should never believe a finding reported only **once**
  - **Error** committed in the study

Criteria for the causal nature…

III. Time sequence (temporal relationship)

- A cause must precede an effect
- Ex. Cigarette smoking precedes the lung cancer

IV. Strength of the association

- Quantitative strength
- Study design

Criteria for the causal nature…

V. Dose-response relationship

- As the dose of exposure increases, the risk of disease also increases.
- **Absence** of a dose-response relationship does not necessarily **rule out** a causal relationship
- In some cases in which a threshold may exist,
  - No disease may develop up to a certain level of exposure (a threshold)

Criteria for the causal nature…

V. Specificity of the association

- When a certain **exposure** is associated with only one disease
- **Weakest** of all guidelines

VI. Cessation of Exposure

- If a factor is a cause of a disease, we would expect the risk of the disease to **decline** when **exposure** to the factor is **reduced** or eliminated.

Types of causal relationship

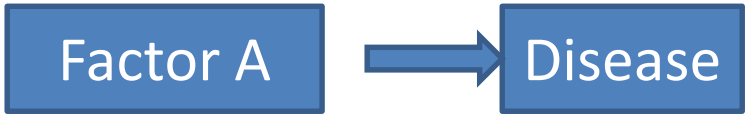
- A causal pathway can be either ***direct*** or ***indirect***
- ***Direct*** **causation**
  - A Factor directly causes a disease without any intermediate step
  - **Factor →Disease**
- **In *indirect* causation**
  - A factor causes a disease, but only through an **intermediate** step or steps.
  - **Factor** →Step 1 → Step 2→**Disease**

Types of causal relationship…

- In human biology, **intermediate** steps are virtually always present in any causal process.
- There are **four** types of possible causal relationships
  - Necessary and sufficient
  - Necessary, but not sufficient
  - Sufficient, but not necessary
  - Neither sufficient nor necessary

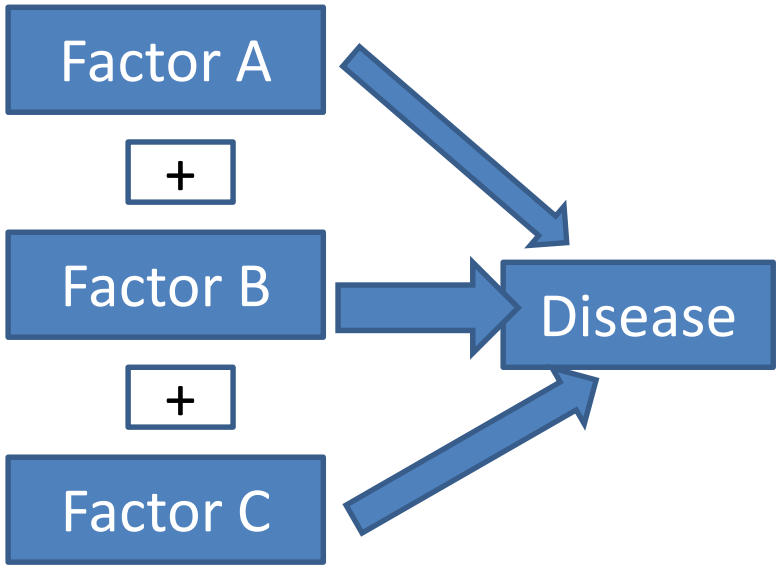
Types of causal relationship…

- **Necessary and sufficient**
  - a **factor** is both necessary and sufficient for producing the disease.
  - Without that factor, the disease never develops (the factor is necessary)
  - in the presence of that factor, the disease always develops (the factor is sufficient)
  - This situation rarely if ever occurs



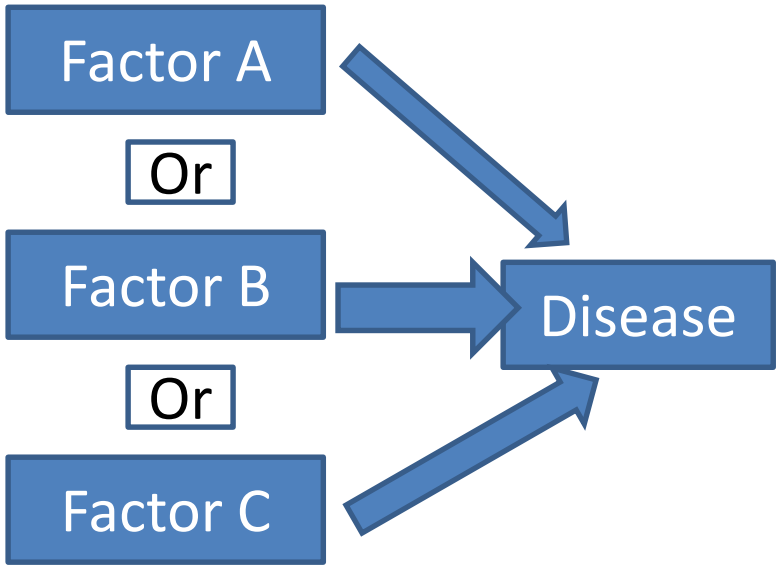
Types of causal relationship….

- **Necessary, But Not Sufficient**
  - Each factor is necessary, but not, in itself, sufficient to cause the disease
  - E.g. in **tuberculosis**, the ***tubercle bacillus*** is clearly a necessary factor, even though its presence may not be sufficient to produce the disease in every infected individual.



Types of causal relationship…

- **Sufficient But Not Necessary**
  - the **factor alone** can produce the disease, but so can other factors that are acting alone
  - E.g. either **radiation** exposure or **benzene** exposure can each produce **leukemia** without the presence of the other.



Types of causal relationship…

- **Neither Sufficient Nor Necessary**
  - a factor, by itself, is neither sufficient nor necessary to produce disease
  - This is a more complex model
  - probably **most accurately** represents the causal relationships that operate in most chronic diseases.